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(54) A nasal spray containing a steroid and a antihistamine

(57) The present invention relates to novel nasal spray compositions comprising a safe and effective amount of a glucocorticosteroid and an antihistamine possessing leukotriene inhibiting properties.

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made at 25°C unless otherwise specified.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention contain the essential components as well as various optional components as indicated below.

More specifically, the compositions of the instant invention are for nasal administration and contain a therapeutically effective amount of the herein described pharmaceutical agents. They are preferably provided as isotonic aqueous solutions, suspensions or viscous compositions which may be buffered to a selected pH.

Essential Ingredients

Glucocorticoid Agents

Agents within this class have potent glucocorticoid activity and weak mineralocorticoid activity. Glucocorticoid agents most useful to the present invention include those selected from the group consisting of beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof.

When used in the compositions of the present invention, the glucocorticoid component is preferably present at a concentration of from about 0.001% to about 0.2%, more preferably from about 0.01% to about 0.1%.

Leukotriene Inhibiting, Antihistaminic Agents

Antihistamines useful to the present invention are histamine H-1 receptor antagonists which also reduce mammalian leukotriene levels. Such H-1 receptor antihistamines may be selected from among the following groups of antihistamines: piperazines, phenothiazines, piperidines.

Examples of useful leukotriene inhibiting antihistamines include cetirizine, loratadine, azelastine and the like, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. When used in the compositions of the present invention, the antihistamine component is preferably present at a concentration of from about 0.01% to about 4.0%. more preferably from about 0.01% to about 1%.

Pharmaceutically-Acceptable Aqueous Nasal Carrier.

One other essential component of the present invention is a pharmaceutically-acceptable intranasal carrier. Preferred for use herein are aqueous saline solution carriers. These solutions which generally contain sodium chloride as the salt are fully described in Remington's Pharmaceutical Sciences, 17th edition (1985) p. 835, which is herein incorporated by reference. The salt is present in the solution at a level of about 0.01% to about 2%, preferably from about 0.5% to about 1.0%.

The combination of any of the above described antihistamines and glucocorticoids can be conveniently administered nasally to warm-blooded animals to elicit the desired therapeutic response by formulating it into a nasal dosage form, together with a nontoxic pharmaceutically-acceptable nasal carrier. Suitable nontoxic pharmaceutically-acceptable nasal carriers are known to those skilled in the art and are also fully disclosed in Remington's Pharmaceutical Sciences, 17th edition, 1985. Obviously, the choice of suitable carrier forms will depend on the exact nature of the particular nasal dosage form required, e.g., whether the drug(s) is to be formulated into a nasal solution (for use as drops or as a spray), a nasal suspension, a nasal ointment, a nasal gel or another nasal form. Preferred nasal dosage forms are solutions, suspensions and gels, which normally contain sodium chloride in a major amount of water (preferably purified water) in addition to the antihistamine and glucocorticoid. Minor amounts of other ingredients such as pH adjusters (e.g., an acid such as HCl), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present. Most preferably, the nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid.

Preferably the composition is applied to the nasal mucosa via topical application of a safe and effective amount of the composition to treat nasal symptoms. The amount of the antihistamine and glucocorticoid combination and frequency of topical application to the nasal mucosa may vary, depending upon personal or medical needs, but it is suggested, as an example, that topical application range from about once per day to about four times daily, preferably twice daily, most preferably once daily. As a practical matter the selected therapeutic compositions will normally be prepared in unit dosage forms or actuations to contain therapeutically effective amounts of the selected antihistamine and glucocorticoid combination. In specific instances fractions of these dosage units or multiple dosage units will be employed. Typically, dosage units may be prepared to deliver from about 0.5 mcg to about 100 mcg of the glucocorticoid

lose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, carboxyvinyl polymer, carbomer, and the like or pharmaceutical salts thereof. Mixtures of such thickening agents may also be used. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents.

Preferred compositions within the scope of this invention will contain from about 0.01% to about 5% of a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of pharmaceutically-acceptable humectants can be employed including, for example sorbitol, propylene glycol, polyethylene glycol, glycerol or mixtures thereof. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

Enhanced absorption across the nasal membrane can be accomplished employing a therapeutically acceptable surfactant. Typical useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Polysorbate 80, Polyoxyl 40 Stearate, Polyoxylethylene 50 Stearate and Octoxynol, as well as Oxyethylated tertiary octyl phenol formaldehyde polymer (available from Sterling Organics as tyloxapol) or mixtures thereof. The usual concentration is from 0.5% to 10% based on the total weight.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions of the present invention. Benzyl alcohol is suitable, although a variety of preservatives including, for example, parabens, phenylethyl alcohol, thimerosal, chlorobutanol, phenylmecuric acetate or benzalkonium chloride may also be employed. The most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA. A suitable concentration of the preservative will be from 0.001% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected Mixtures of these preservatives may also be used.

Other Optional Components. A variety of additional ingredients may be added to the emulsion compositions of the present invention. These additional ingredients include various polymers for aiding the film-forming properties and substantivity of the formulation, antioxidants, and agents suitable for aesthetic purposes such as fragrances, pigments, and colorings.

The compositions can also contain low levels of insoluble ingredients added, for example for visual effect purposes, e.g. thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl) phenyl 4-alkyl(oxy)benzoates available from Hallcrest, Glenview, Illinois 60025. U.S.A. Mixtures of these ingredients may also be used.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Example I

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described below.

Component	Wgt %
beclomethasone diproprionate, monohydrate	0.042
loratadine	0.200
avicel RC - 591[1]	1.200
dextrose	5.100
polysorbate 80	0.025
benzalkonium chloride	0.040
phenylethyl alcohol	0.250
distilled water	q.s. to vol.

[1] microcrystalline cellulose and sodium carboxymethyl cellulose, supplied by FMC corporation.

In an appropriately-sized vessel, the dextrose, polysorbate 80 and benzalkonium chloride are added one at a time to water with mixing, allowing each to dissolve or completely disperse before adding the next. To this is added, with mixing, a premixed slurry of the avicel and water. Upon forming a uniform solution, the beclomethasone, loratadine

flunisolide, triamcinolone. fluticasone. mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof:

b) a safe and effective amount of a leukotriene inhibiting antihistamine selected from the group consisting of cetirizine, loratadine. azelastine. pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof: and

c.) an intranasal carrier.

2. A composition according to Claim 1 in the form of an isotonic aqueous solution

3. A composition according to Claim 1 or 2 wherein the glucocorticoid is selected from the group consisting of beclomethasone, budesonide, fluticasone and mixtures thereof.

4. A pharmaceutical composition according to any of Claims 1-3, which further comprises a sympathomimetic amine selected from the group consisting of pseudoephedrine, desoxyephedrine, propylhexedrine, phenylpropanolamine, xylometazoline, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof.

5. A pharmaceutical composition according to any of Claims 1-4, which further comprises a non-steroidal anti inflammatory agent, or optically active racemates thereof and mixtures thereof.

6. A pharmaceutical composition according to any of Claims 1-5. which further comprises a lipoxygenase inhibitor or antagonist, a leukotriene receptor antagonist, a nonopiate analgesic, a mucolytic, an antiallergic, and pharmaceutically acceptable salts thereof and mixtures thereof.

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EUROPEAN SEARCH REPORT

Application Number
EP 96 30 8852

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	EP 0 605 203 A (SENJU PHARMA CO) 6 July 1994 * the whole document * -----	1-6	(A61K31/58, A61K31:495), (A61K31/58, A61K31:445)

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	1 April 1997	Herrera, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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